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Intracellular Signaling Pathways

Program/Abstract # 86
A re-evaluation of two key reagents for *in vivo* studies of Wnt signaling

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Conditional mutations and transcription-based reporters are important new tools for exploring the dynamic functions of biological pathways in vivo. While studying the role of the Wnt signaling pathway in cartilage we observed that the beta-catenin dependent reporter TOPGAL was expressed in chondrocytes in which beta-catenin was conditionally inactivated using a Col2a1:cre driver. Here we show that in these embryos recombination is complete and full-length beta-catenin protein is absent in chondrocytes. Although a null allele in this context, the recombined beta-catenin locus produces stable transcripts that encode truncated proteins. The truncated protein alone fails to activate TOPFLASH, but it strongly potentiates reporter activity in the presence of beta-catenin. Together, these data show that each mouse model exhibits specific undesirable properties, findings that strongly suggest the need for specific standards to ensure proper validation of this new generation of genetic tools.

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Program/Abstract # 87
The role of the dual Bmp/Wnt inhibitor Sostdc1 in adult pancreas function

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Recent studies have revealed the roles of bone morphogenetic protein (Bmp) and Wnt signaling in the positive regulation of pancreatic β cell function. Bmp4 signaling through Bmp receptor 1a (Bmpr1a) in the pancreatic epithelium positively regulates expression of genes involved in insulin production, synthesis, and glucose sensing and metabolism. Wnt signaling through the Lrp5 receptor regulates glucose homeostasis and insulin secretion, and Wnt target genes include those involved in cell cycle regulation and β cell function. Loss of either Bmp or Wnt signaling in the pancreatic epithelium results in impaired glucose homeostasis, decreased insulin secretion, and decreased expression of genes involved in islet function. Through microarray analysis of gene expression in the hepatocyte nuclear factor (Hnf) 6 mouse model of lean, non-immune mediated diabetes, we identified a 2-fold up-regulation of the dual Bmp and Wnt inhibitor Sostdc1 in the pancreata of postnatal day (p) 1 animals. We have investigated whether loss of Sostdc1 improves β cell function and insulin secretion using a global knockout (KO) mouse model. The role of Sostdc1 or other Bmp and Wnt inhibitors has not yet been studied in the adult pancreas, but aberrant Bmp and Wnt signaling have been observed in mouse models of diabetes and obesity. We have found that adult male Sostdc1 KO animals exhibit significantly lower ad lib feeding glucose levels compared to WT littermates. When placed on high fat diet (HFD) for 8 weeks, a subset of male KO animals show significantly improved insulin secretion during islet perifusion, and after 12 weeks HFD show significantly improved glucose clearance during an intraperitoneal glucose tolerance test (IPGTT). We are currently determining whether genetic background contributes to the severity of the Sostdc1 KO phenotype. Additionally, we have observed that Sostdc1 KO animals with fasting blood glucose of <125 mg/dl trend toward higher β cell mass after 12 weeks of HFD. Furthermore, we have observed alterations in expression of Bmp-responsive genes and expression of Bmp/Wnt modulators in islets isolated from Sostdc1 KO animals. These results suggest that relieving Bmp/Wnt inhibition can improve β cell function, possibly through alteration of gene expression.

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Program/Abstract # 88
Axin promotes canonical Wnt signaling in the late primitive streak of mouse embryos

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Recently, small molecules that increase the stability of Axin protein and reduce the responsiveness to Wnt ligand of cells in culture have been identified. However, we have carried out experiments demonstrating that the effect of Axin stabilization in vivo varies between cells. Axin proteins are negative regulators of the canonical Wnt signal transduction pathway, serving as a scaffold for the cytosolic β-catenin destruction complex. Drosophila genetics has shown that Axin levels may be rate limiting in the ability of the complex to degrade β-Catenin; therefore, a tight regulation of Axin levels is required for appropriate signaling in the developing embryo. Although Axin2 null animals are viable, we identified an ENU-induced recessive allele of Axin2, canp, that causes midgestation lethality in homozygotes. We show that the Axin2 canp protein is more stable than wild type and, as predicted for an increased level of a negative regulator, the Axin2 canp mutation leads to decreased Wnt signaling in most tissues, which can account for most of the of Axin2 canp phenotypes. In contrast, there is a paradoxical increase in